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REal-LIfe Evidence of stroke prevention in patients with atrial Fibrillation — The RELIEF study

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Rivaroxaban has been shown effective in reducing the risk of stroke in patients with non-valvular atrial fibrillation (NVAF) in a randomized controlled trial (RCT) [1]. However, scarce data comparing real-life outcomes between rivaroxaban and vitamin K antagonist (VKA) users with NVAF are available [2]. The objective of the 'REal-LIfe Evidence on stroke prevention in patients with atrial Fibrillation' (RELIEF) study was to compare the effectiveness of newly-initiated rivaroxaban or VKA therapy among NVAF patients in Germany.

The RELIEF study was a retrospective study performed in German outpatients using data from the Primary Care Physician panel (representing 1205 practices/1409 physicians) of a patient-level longitudinal electronic medical record (EMR) database (IMS Disease Analyzer) [3]. To be included, patients had to be newly-initiated on rivaroxaban or a VKA between 1/2012 and 10/2013, ≥18 years-of-age on the day of the first qualifying anticoagulant prescription (index date), have a diagnosis of NVAF on the index date or any time during the 365-days prior, have follow-up ≥360-days after the index date and exhibit evidence of patient activity during the 90-days prior to the index date. A 12-month pre-index period was used to identify patient co-morbidities and prior medication use. Patients with valvular AF, experiencing a prior cardiovascular event as defined in the composite endpoint, receiving an oral anticoagulant (OAC) before the index date, prescribed >1 OAC on the index date or during follow-up or receiving rivaroxaban at a dose and/or schedule inconsistent with approved labeling were excluded. Since analysis of only anonymized data was performed, this study was exempted from institutional review board oversight.

Potentially eligible rivaroxaban (n = 1046) and VKA (n = 4062) patients were 1:1 propensity score-matched to generate an analysis cohort with minimal differences in baseline characteristics [4]. Residual differences in characteristics between matched cohorts were assessed by calculating standardized differences, with differences of <10% considered balanced [5]. Patients were matched on age, gender, CHA2DS2-VASc risk score and the number of co-morbidities.

The a priori primary endpoint was the time-to-composite of ischemic stroke, transient ischemic attack, intracerebral hemorrhage, other non-traumatic intracranial hemorrhage including subdural hemorrhage and myocardial infarction within one-year of treatment initiation. The incidence of events was reported as the number of events/100 person-years and calculated as the number of patients with ≥1 documented event divided by the entire time at risk of the respective cohort.

Baseline characteristics of patients were analyzed using descriptive statistics. A Cox proportional hazard analysis was performed to calculate the hazard ratio (HR) with 95% confidence intervals (CIs) for developing the primary endpoint between the matched cohorts within the first-year after treatment initiation. Statistical analyses were performed using SAS v9.3 (SAS Inc., Cary, NC, USA).

Following propensity score-matching, 1039 rivaroxaban and 1039 VKA users were matched. Characteristics of the cohorts are in Table 1. No characteristic exhibited a standardized difference >10%.

In total, 57 events were identified during follow-up (Table 2). The incidence of the primary endpoint was lower in rivaroxaban compared with VKA users (1.97 vs. 3.68 events/100 person-years) corresponding to a hazard ratio of 0.54 (95%CI = 0.31–0.92) in the time-to-event analysis. Rates of individual endpoints were numerically less frequent in the rivaroxaban cohort.

This study used real-life EMR data from Germany to compare the effectiveness of rivaroxaban and VKA therapy in NVAF patients. Rivaroxaban use was associated with a lower incidence of developing the primary endpoint, as well as individual components. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) [1] failed to demonstrate a reduction in ischemic stroke

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Table 1
Characteristics of included patients (matched cohorts).

Parameter	Rivaroxaban N = 1039	VKA N = 1039
	n (%)	n (%)
Age in years, mean (SD)	74.0 (10.7)	74.4 (9.9)
Gender, % male	538 (51.8)	538 (51.8)
Relevant co-morbidities		
Hypertension (ICD-10 I10)	835 (80.4)	846 (81.4)
Diabetes mellitus (ICD-10 E10-14)	334 (32.1)	366 (35.2)
Renal failure (N17–19)	110 (10.6)	133 (12.8)
Deep vein thrombosis (ICD-10 I80-82 without I80.0)	81 (7.8)	66 (6.4)
Unstable angina (ICD-10 I20)	76 (7.3)	64 (6.2)
Hyperthyreoidea (ICD-10 E05)	65 (6.3)	61 (5.9)
Pulmonary embolism (ICD-10 I26)	22 (2.1)	30 (2.9)
Congestive heart failure (ICD-10 I50)	29 (2.8)	28 (2.7)
Functional dyspepsia (ICD-10 K30)	21 (2.0)	20 (1.9)
Stroke risk scores		
CHADS2 score, mean (SD)	1.7 (1.0)	1.8 (0.9)
CHA2DS2-VASc score, mean (SD)	3.9 (1.5)	3.9 (1.4)
Bleeding risk score		
ATRIA modified*, mean (SD)	2.1 (1.7)	2.1 (1.7)
Time period in days between NVAF diagnosis and start of OAC treatment (days), mean (SD)	18.5 (47.4)	29.3 (61.7)
History of cardiovascular drug use		
Anti-arrhythmics	140 (13.5)	113 (10.9)
Beta blockers	792 (76.2)	795 (76.5)
ACE inhibitors	453 (43.6)	537 (51.7)
ARBs	294 (28.3)	246 (23.7)
Ca channel blockers	311 (29.9)	349 (33.6)
Diuretics	416 (40.0)	484 (46.6)
Anti-platelet drugs	292 (28.1)	258 (24.8)

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; Ca = calcium; ICD-10 = International Classification on Diseases-10th revision; SD = standard deviation; SHI = statutory health insurance; VKA = vitamin K antagonist.
* The ATRIA score was calculated based on ICD-10 codes; because for some conditions like anemia respective laboratory values were not available.

(HR = 0.94, 95%CI = 0.75–1.17) between rivaroxaban and warfarin users. There are, however, plausible explanations for the differences in findings between these studies. In ROCKET-AF, Western European patients had a mean time-in-the therapeutic international normalized ratio (INR) range (TTR) of ~63%; a value similar to most RCTs [1,6]. However, a meta-analysis suggests that TTR is 9% (95%CI = 4–14%) lower in community compared with RCT-treated patients [7]. It is possible that the TTR in this real-life German population was lower than in ROCKET-AF; reducing VKA effectiveness. This may have been particularly true in the first months of VKA initiation [7], which is consistent with the shorter median time-to-event observed with VKA (vs. rivaroxaban) in our study. Although the IMS database contains INR data; laboratory values were not available for all patients and we could not formally test this hypothesis. A second explanation for the favorable relative effectiveness of rivaroxaban in the real-world is the higher likelihood of discontinuation with VKAs compared with non-VKA OACs [2,8]. Finally, the predominant use of phenprocoumon in Germany may have played a role.

Laliberte and colleagues [2] published the only other real-life comparative effectiveness study of rivaroxaban vs. VKA in NVAF patients. These investigators utilized US healthcare claims from 5/2011–7/2012, and matched 3654 rivaroxaban and 14,616 warfarin users with a CHADS2 score ≥ 1. Their data suggested a reduction in stroke or systemic embolism (HR = 0.77, 95%CI = 0.55–1.09) with rivaroxaban compared with VKA therapy, although this result did not reach statistical significance.

There are some limitations to consider. First, a small number of primary events were observed. Second, common to administrative claims/EMR analyses, data may contain coding inaccuracies/missing data that can result in biases and the potential of residual confounding cannot be excluded. Next, although sometimes used in real-world practice for NVAF (e.g., very elderly and/or renal dysfunction), we excluded patients receiving <15 mg and/or twice daily doses of rivaroxaban because these are not consistent with rivaroxaban's labeling for NVAF and maybe confused with orthopedic indications within an administrative claims database. Finally, to allow insights on the effectiveness of rivaroxaban compared with VKA within the first-year after treatment initiation, the current analysis used only cohorts of patients with a follow-up of ≥360-days. For this reason bias in either cohort due to the exclusion of patients with lesser follow-up cannot be ruled out.

In conclusion, this study suggests rivaroxaban is associated with favorable effectiveness in NVAF patients without previous events compared to a VKA when utilized in a real-life setting. Further analysis containing INR and effectiveness data is warranted.

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Conflicts of interest

CIC has received grant funding and consulting fees from Bayer Pharma AG, Janssen Pharmaceuticals, Boehringer Ingelheim and Pfizer. MA has received consulting fees and speaker honoraria from Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers-Squibb, Daichii-Sankyo and Pfizer. BE's institution (IMS Health) received funding from Bayer for the preparation of study documents and/or the performance of statistical analyses. TE is employee of Bayer Pharma AG.

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Table 2
Composite endpoint and individual components.

Endpoint	Rivaroxaban N = 1039	VKA N = 1039
	n (%)	n (%)
Composite endpoint — incidence per 100 patient years	20 (1.97)	37 (3.68)
Median time to primary event (days) in patients with events	172.5	155.0
Composite endpoint rivaroxaban vs. VKA; hazard ratio (95%CI, p value)	**0.536 (0.311–0.923, p = 0.0245)**	
Single endpoints (first event) — incidence per 100 patient years*		
Ischemic stroke (ICD-10 I63)	7 (0.69)	16 (1.58)
TIA (ICD-10 G45 without G45.3)	6 (0.59)	11 (1.08)
Intracerebral hemorrhage (ICD-10 I61)	1 (0.10)	3 (0.29)
Other non-traumatic intracranial hemorrhage including subdural hemorrhage (ICD-10 I62)	0 (0.00)	1 (0.10)
MI (acute and subsequent; ICD-10 I21,I22)	6 (0.59)	7 (0.69)

CI = confidence interval; ICD-10 = International Classification on Diseases-10th revision; MI = myocardial infarction; TIA = transient ischemic attack; VKA = vitamin K antagonist.
* One patient in the VKA cohort with more than one single endpoint recorded at the same day.

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